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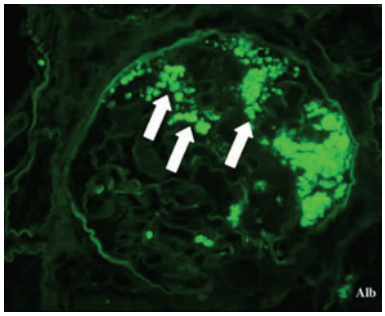
Collapsing glomerulosclerosis and nephrotic syndrome in hemophagocytic syndrome

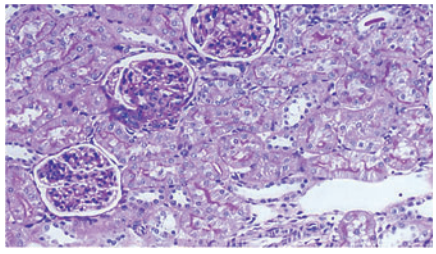
In hemophagocytic syndrome, the bone marrow and other organs are infiltrated by activated macrophages with internalized red cells. The syndrome is seen in many



genetic diseases of the immune system, where activation of a large number of histiocytes causes high levels of cytokine production by the activated macrophages themselves or other immune cells. In their study, Thaunat *et al*. investigated a number of such patients who developed the nephrotic syndrome in association with the activated macrophage entity. They found on renal biopsy that acute tubular necrosis was associated with collapsing glomerulopathy in half of their patients, all Africans with negative HIV serology. Some had minimal change glomerulopathy, and others had microangiopathic changes. The prognosis was very poor in most patients. This phenomenon represents a new cause of nephrotic syndrome and collapsing glomerulosclerosis. The involvement of the immune system in the original disease suggests that cytokines produced by the activated cells might have etiologic significance. **See page 1892.**

Inhomogeneity of glomerular blood flow in glomerulonephritis

Disturbances in glomerular hemodynamics are central to the causation of glomerulosclerosis, but the details of glomerular blood flow in these situations remain unclear. As they report in this issue, Kawamura *et al*. induced glomerulonephritis using anti-Thy-1 antibody followed by nephrectomy. They then subjected the Munich-Wistar rats, which had surface glomeruli, to a study of red-cell velocity in different regions of the glomerular tufts. As the authors previously found, this form of glomerular injury was also associated with the formation of aneurysms in the glomerulus. Fluorescently labeled red cells were then injected, and the velocity was measured in two fixed points in several glomeruli using laser-scanning confocal microscopy. Glomeruli that were affected by the anti-Thy-1 antibody had more inhomogeneous flow with wide differences between the two points of measurement in each glomerulus. In some glomeruli, the



flow stopped and returned in a jerky manner. It is obvious that this disturbance of blood flow is an example of turbulent flow. Anti-Thy-1 causes an irreversible sclerosis and proteinuria early in the course of the disease. Whether the turbulent flow is a consequence or a cause of the glomerulosclerosis is a new question that needs to be evaluated. **See page 1792.**

Regulated intramembrane proteolysis

A surprising development in cell biology has been the identification of a number of membrane-bound proteases that digest membrane proteins and whose catalytic domain is buried in the membrane. Biemesderfer reviewed this subject by taking as a model the proteolysis of megalin in the proximal tubule. Intramembrane proteolysis was best characterized in the Notch signaling pathway, wherein removal of the extracellular domain was accomplished by one protease. This allowed the second one, γ-secretase, to clip off the cytoplasmic domain, which then went to the nucleus to activate transcription. Megalin was also digested by γ-secretase after activation by a protein kinase C-activated shedding of the extracellular domain. As megalin is the major route of albumin uptake into the proximal tubule, it is likely that this process of production of a cytoplasmic domain plays a part in the gene activation seen after protein absorption. The fact that the cytoplasmic domain of megalin eventually finds its way to the nucleus suggests that this pathway exists in the kidney. **See page 1717**.